

Mini-review

Preventive effects of drinking green tea on cancer and cardiovascular disease: Epidemiological evidence for multiple targeting prevention

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Abstract. The significance of drinking green tea in prevention of two of the main lifestyle-related diseases, cancer and cardiovascular disease, was demonstrated in terms of a prospective cohort study on a total of 8,552 general residents in Saitama Prefecture, Japan. On the basis of the follow-up study, we revealed decreased relative risk of cancer incidence for those consuming over 10 cups a day, compared with those consuming below 3 cups: 0.54 (95% confidence interval, 0.22–1.34) for men, 0.57 (0.34–0.98) for women, and 0.59 (0.35–0.98) for both sexes. Furthermore, a significant delay in cancer onset was associated with increased consumption of green tea. Next, decreased relative risk of death from cardiovascular disease was 0.58 (0.34–0.99) for men, 0.82 (0.49–1.38) for women, and 0.72 (0.60–1.04) for members of both sexes consuming over 10 cups a day. Finally, we evaluated the life-prolonging effects of drinking green tea on cumulative survival, using the life table.

Keywords: Green tea, cancer, cardiovascular disease, prospective cohort study

1. Introduction

Green tea has recently obtained significant acceptance as a cancer preventive, on the basis of numerous studies from around the world, which have been accumulating since 1987, when Dr. H. Fujiki's group for the first time reported the cancer-preventive activity of (-)-epigallocatechin gallate (EGCG), the main constituent of green tea polyphenols [1]. Subsequent laboratory studies have revealed that EGCG or green tea extract in drinking water inhibited carcinogenesis in various organs in rodents [2–4]. In addition to the experimental evidence, our prospective cohort study previously reported the cancer-preventive effects of drinking green tea on the basis of a nine-year follow-up study (384 cancer cases) [5]. Our Phase I trial with green tea tablets found that blood examination showed no adverse effects among the participants [6].

On the other hand, tea polyphenols were reported to reduce the levels of serum lipids in animal models, implying the preventive effects of green tea on cardiovascular disease [7,8]. We previously reported

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that drinking green tea resulted in lower serum levels of total cholesterol and triglyceride, along with a decreased atherogenic index, in terms of a cross sectional analysis of the prospective cohort study [9]; a further study using follow-up data remains to be reported.

In this paper we demonstrated the significance of green tea not only in prevention of cancer and cardiovascular disease, but also in prolonging life activity, indicating that green tea is effective for multiple targeting prevention.

2. Subjects and methods

In 1986 we began a prospective cohort study in residents over 40 years of age in a town in Saitama Prefecture, Japan. We used a self-administered questionnaire covering 90 lifestyle factors, where green tea consumption was categorized as below 3, 4–9, and over 10 cups a day. The questionnaire covered a total of 8,552 individuals. The details were described elsewhere [5]. Our eleven-year follow-up study from 1986 to 1997 found a total of 488 cancer cases. The most frequent cancers among both sexes were, in order, cancers of the stomach (140), lung (69), colorectum (60), and liver (35).

In the follow-up study, we surveyed death from all causes by death certificate from 1986 to 1997. A total of 1,109 deaths from all causes (338, 222, 193, and 356 deaths from cancer, cardiovascular disease, cerebrovascular disease, and other causes, respectively) were used in the analysis of cumulative proportion surviving. In the analysis of green tea and cardiovascular disease, we added 52 cardiovascular deaths in 1998 and 1999 to those from 1986 to 1997, for a total of 274 deaths from cardiovascular disease (ICD-9: 390–429).

3. Results

3.1. Age-standardized incidence rates and relative risk of cancer incidence

The overall cancer incidence rates, specifically, truncated age-standardized cancer incidence rates, were calculated by daily consumption of green tea, using a truncated world population, age over 40 years per 32,000 per annum. The rates ($\pm$ SE) among women strongly indicate that high consumption (over 10 cups a day) of green tea resulted in a significant reduction of cancer incidence by about 40%: 116.5 ± 15.6 , 159.6 ± 12.7 , and 81.6 ± 18.6 for those consuming below 3, 4–9, and over 10 cups a day, respectively. On the other hand, men revealed an increased cancer incidence among those consuming over 10 cups a day: 190.0 ± 23.3 , 193.6 ± 17.2 , 264.2 ± 32.0 for those consuming below 3, 4–9, and over 10 cups a day, respectively. In men, an increased percentage of current smokers and their cigarette consumption was observed among those consuming the most green tea, compared with other groups (data not shown). Thus, the deleterious effects of cigarette smoking seem to cancel the benefits of drinking green tea. In fact, male non-smokers (never and ex-smokers) revealed a decreased cancer incidence associated with high consumption of green tea: 185.5 ± 35.5 , 194.0 ± 27.6 , 154.8 ± 45.2 for those consuming below 3, 4–9, and over 10 cups a day, respectively.

We then evaluated cancer risk by considering differences in lifestyle. Relative risk of cancer incidence by consumption of green tea was estimated in Table 1 by the Cox proportional hazard model, adjusting for the potent confounding factors. Women who consumed over 10 cups a day revealed a significantly decreased risk of 0.57, taking the risk of those consuming below 3 cups a day as reference. Men also showed a reduction in relative risk with increased consumption of green tea. Combining data for men

Table 1
Relative risk^a of cancer incidence by daily consumption of green tea

	Consumption of green tea (cups/day)		
	≤ 3	4–9	≥ 10
Men	1.0	1.00 (0.50–2.04) ^b	0.54 (0.22–1.34)
Women	1.0	0.92 (0.64–1.31)	0.57 (0.34–0.98)
Both sexes	1.0	0.81 (0.52–1.27)	0.59 (0.35–0.98)

^aAdjusted for cigarette smoking, alcohol consumption, intake of green and yellow vegetables, and intake of rice, using age as the fundamental time variable.

^bIn parentheses, 95% confidence interval.

Table 2
Mean age (± SE, years) at cancer onset by daily consumption of green tea among 488 cancer patients found in the follow-up study

	Consumption of green tea (cups/day)			All categories
	≤ 3	4–9	≥ 10	
Men	65.7 ± 0.6 (69) ^a	68.0 ± 0.9 (130)	68.9 ± 1.0 (86)	67.7 ± 0.6 (285)
Never smokers ^b	70.2 ± 3.7 (14)	71.4 ± 2.2 (19)	74.1 ± 2.5 (6)	71.4 ± 1.7 (39)
Current smokers	62.6 ± 1.6 (40)	67.3 ± 1.1 (76)	68.6 ± 1.1 (70)	66.8 ± 0.7 (186)
Women	68.3 ± 1.6 (58)	67.5 ± 1.1 (117)	74.5 ± 2.0 (28)	68.7 ± 0.9 (203)
Both sexes	66.9 ± 1.0 (127)	67.7 ± 0.7 (247)	70.2 ± 0.9 (114)	68.1 ± 0.5 (488)

^aIn parenthesis, number of patients.

^bExcluding ex-smokers.

and women, both sexes revealed a significantly decreased risk of 0.59 associated with high consumption of green tea.

We next analyzed the cancer-preventive effects of green tea by organs. Green tea most significantly exerted its preventive effects on lung cancer in both sexes, with a relative risk of 0.33 (95% CI, 0.11–0.94) among those consuming over 10 cups a day, adjusting for sex and lifestyle factors. High consumption of green tea showed decreased relative risk of 0.56 (0.22–1.40), 0.53 (0.17–1.57) and 0.69 (0.23–1.88) for cancers of the colorectum, liver, and stomach, respectively. This epidemiological observation showed close correlation with the target organs of EGCG or green tea extract in rodent carcinogenesis experiments [2–4].

3.2. Age at cancer onset

Analysis of mean age at cancer onset among the 488 cancer patients found in the follow-up study revealed that increased consumption of green tea was associated with delay of cancer onset (Table 2). Mean age at cancer onset among female patients consuming over 10 cups a day was 6.2 years higher than that among those consuming below 3 cups a day ($P < 0.01$). Among male patients, the difference in mean age at cancer onset by consumption of green tea was 3.2 years, possibly being influenced by cigarette smoking.

We found that cigarette smoking was associated with earlier onset of cancer ($P < 0.01$): mean age ± SE at cancer onset was 66.8 ± 0.7, 68.2 ± 1.3, and 71.4 ± 1.7 years in 186 male current smoker patients, 60 ex-smoker patients, and 39 never-smoker patients, respectively. Thus, earlier onset of cancer among smokers included in the highest consumption group of green tea cancelled the effects of green tea on age at cancer onset. In fact, delay of cancer onset was found in both male never and current smoker patients

Table 3
Serum concentration (Mean $\pm$ SE, nmol/ml) of lipid peroxides (thiobarbituric assay) among male smokers by consumption of green tea

	Consumption of green tea (cups/day)		
	≤ 3	4–9	≥ 10
Current smokers	9.38 $\pm$ 0.23	8.87 $\pm$ 0.18	8.23 $\pm$ 0.20 ^a
Smokers consuming > 20 cigarettes a day ^c	10.30 $\pm$ 0.55	9.79 $\pm$ 0.43	7.79 $\pm$ 0.40 ^b

^a $P < 0.01$, compared with those in ≤ 3 cups; $P = 0.1$ after adjustment for age and cigarette consumption.

^b $P < 0.01$, compared with those in ≤ 3 cups; $P < 0.05$ after adjustment for age and cigarette consumption.

^c The upper quartile in distribution of cigarettes consumed a day (177 smokers).

in association with increased consumption of green tea ($P < 0.05$ for current smokers, Table 2). Our theoretical model predicted that delay of cancer onset by 5, 10, and 15 years generates a reduction of 25, 50, and 70% in cancer incidence, respectively.

3.3. Serum risk markers and relative risk of cardiovascular death

We previously reported an inverse association between consumption of green tea and serum risk markers for cardiovascular disease, in terms of a cross sectional analysis of 3,625 cohort members, 1,371 men, who gave peripheral blood samples at baseline [9]. A more detailed analysis including female subjects revealed: Decreased serum levels of total cholesterol were found among men with increased consumption of green tea, although this lowering effect was not observed among postmenopausal women; Decreased serum triglyceride and atherogenic index were consistently observed among men and women with increased consumption of green tea. Drinking green tea influenced not only serum levels of lipids and lipoproteins but also the oxidative status of serum lipids. Serum levels of lipid peroxides among 766 current smokers (mean $\pm$ SE, 8.83 $\pm$ 0.12 nmol/ml) were higher than those (8.37 $\pm$ 0.21) among 197 never smokers; smokers consuming over 10 cups a day revealed significantly decreased levels of serum lipid peroxides, compared with those consuming lower amounts (Table 3). The reduction of serum lipid peroxides was more remarked among smokers who consumed > 20 cigarettes a day.

We then estimated the relative risk of death from cardiovascular disease by consumption of green tea (Table 4), on the basis of our follow-up study. Men consuming over 10 cups a day revealed a significantly decreased risk of 0.58, adjusted for lifestyle factors; high consumption of green tea prevents cardiovascular death even among smokers with a significantly low relative risk of 0.51. Ten cups (150 ml per cup) of green tea contain 360–540 mg of EGCG or about 1 g of tea polyphenols, which is thought to be the daily required amount for prevention of cancer and cardiovascular disease.

3.4. Cumulative proportion surviving

Deaths from cancer and cardiovascular disease account for about half of all deaths in Japan. Since high consumption of green tea prevents these two major lifestyle-related diseases, we compared mean age at death from all causes by consumption levels of green tea (Table 5): We found that mean age at all death among both men and women became higher with increased consumption of green tea ($P < 0.01$), producing a difference of 3.8 and 6.0 years between the highest and lowest consumption groups, respectively. Combining men and women, the difference in mean age at all death in both sexes was 4.4 years ($P < 0.001$), a result which implies that high consumption of green tea may generate a

Table 4
Relative risk^a of cardiovascular death by daily consumption of green tea

	Consumption of green tea (cups/day)		
	≤ 3	4–9	≥ 10
Men	1.0	1.09 (0.71–1.65) ^b	0.58 (0.34–0.99)
Never smokers	1.0	1.03 (0.41–2.58)	0.49 (0.12–1.97)
Current smokers	1.0	0.96 (0.55–1.67)	0.51 (0.26–0.99)
Women	1.0	0.90 (0.60–1.37)	0.82 (0.49–1.38)
Both sexes	1.0	1.02 (0.76–1.36)	0.72 (0.50–1.04)

^aAdjusted for cigarette smoking, alcohol consumption, intake of meat, and relative body weight, using age as the fundamental time variable.

^bIn parenthesis, 95% confidence interval.

Table 5
Mean age (± SE, years) at death from all causes in the follow-up study by consumption of green tea

	Consumption of green tea (cups/day)			
	≤ 3	4–9	≥ 10	All categories
Men	71.2 ± 1.1 (157) ^a	73.4 ± 0.7 (288)	75.0 ± 0.8 (164)	73.3 ± 0.8 (609)
Women	74.9 ± 1.1 (129)	77.5 ± 0.7 (265)	80.9 ± 0.9 (106)	77.6 ± 0.5 (500)
Both sexes	72.9 ± 0.8 (286)	75.4 ± 0.5 (553)	77.3 ± 0.6 (270)	75.2 ± 0.4 (1109)

^aIn parenthesis, number of deaths.

prolonged lifetime. We, then, studied the life-prolonging effects of drinking large amounts of green tea, in terms of cumulative survival.

We first evaluated the influence of cigarette smoking on cumulative survival by way of example, since cigarette smoking is the most potent well-known risk factor for cancer and cardiovascular disease, providing a scale to compare with the effects of green tea. Percent survivors (± SE) among male never and current smokers were 95 ± 1 and 87 ± 1% for age-period of 40–69 years, 75 ± 3 and 66 ± 2% for 40–79 years, and 50 ± 5 and 46 ± 3% for 40–84 years, respectively. Specifically, cigarette smoking reduced percent survivors at age 84 from 50% among never smokers to 46% among current smokers.

Next, we studied cumulative survival by consumption of green tea (Table 6). In both men and women, we found a significant increase of percent survivors among those consuming over 10 cups a day for each age-period, compared with those consuming smaller amounts. The differences in percent survivors by consumption of green tea increased with age, resulting in 53 and 41% among men, and 69 and 59% among women surviving at age of 84 years. This excess of 12 and 10% in percent survivors at age 84 was greater than the difference of 4% by cigarette smoking.

4. Discussion

Green tea is an acknowledged cancer preventive, specifically in prevention targeting the delay of carcinogenic processes. We demonstrated epidemiological evidence in this report on the basis of our prospective cohort study. Furthermore, various functions of tea polyphenols may generate further benefits to human health other than cancer prevention. Along this line, we examined the association between consumption of green tea and cardiovascular disease and indicated remarkable preventive effects of green tea on the disease.

Table 6
Cumulative proportion surviving ($\pm$ SE, %) by daily consumption of green tea, estimated by the life table obtained from the follow-up study

Age-periods (years)	Consumption of green tea (cups/day)		
	≤ 3	4–9	≥ 10
Men			
40–69	86 $\pm$ 2	90 $\pm$ 1	89 $\pm$ 1
40–79	66 $\pm$ 3	66 $\pm$ 2	71 $\pm$ 3
40–84	41 $\pm$ 4	43 $\pm$ 3	53 $\pm$ 4
Women			
40–69	94 $\pm$ 1	96 $\pm$ 0	97 $\pm$ 1
40–79	77 $\pm$ 3	83 $\pm$ 1	84 $\pm$ 2
40–84	59 $\pm$ 4	66 $\pm$ 2	69 $\pm$ 4

These results encouraged us to further investigate how much green tea contributes to the prolongation of life in a Japanese population who habitually drink large amounts of green tea. The observed excess in percent survivors associated with increased consumption of green tea became larger with age, implying that high consumption of green tea prolongs life activity and thus contributes to long and healthy lives. Green tea can be used as a multiple targeting preventive without toxicity both in the general population where target diseases of prevention are various and sometimes uncertain, and also in high-risk populations with green tea alone or in combination with other disease-specific preventives.

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